Boehringer Ingelheim Pharma KG
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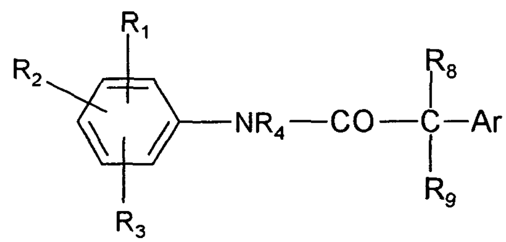
Carboxylic acid amides, the preparation thereof and their use as pharmaceutical compositions

The present invention relates to carboxylic acid amides of general formula



(I),

the tautomers, the stereoisomers, the mixtures, the prodrugs, the derivatives thereof which contain a group that is negatively charged under physiological conditions instead of a carboxy group, and the salts thereof, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases which have valuable properties.

The compounds of the above general formula I wherein Ar denotes a phenyl or naphthyl group substituted by the groups R_5, R_6 and R_7, and R_5 denotes a cyano group, are valuable intermediate products for preparing the corresponding compounds of general formula I wherein R_5 denotes an amidino group optionally substituted by one or two C_{1-3}-alkyl groups. The compounds of the above general formula I with the exception of those compounds wherein Ar denotes a phenyl or naphthyl group substituted by the groups R_5, R_6 and R_7, and R_5 denotes a cyano group, as well as the tautomers, the stereoisomers, the mixtures, the prodrugs, the derivatives thereof which contain a group that is negatively charged under physiological conditions instead of a carboxy group, and the salts thereof, particularly the physiologically acceptable salts thereof with inorganic or organic acids, and the stereoisomers thereof, have valuable pharmacological properties, particularly an antithrombotic activity and an inhibiting effect on factor Xa.

The present application thus relates to the new compounds of the above general formula I and the compound

2-(5-carbamimidoyl-2-hydroxy-phenyl)-N-[3-chloro-4-(pyrrolidin-1-yl-carbonyl)-phenyl]-acetamide,

the preparation thereof, the pharmaceutical compositions containing the pharmacologically effective compounds, their preparation and use.

In the above general formula

R_1 denotes a C_{3-7}-cycloalkyl-carbonyl group wherein

the methylene group in the 3 or 4 position in a C_{5-7}-cycloalkyl-carbonyl group may be replaced by an -NH group wherein

the hydrogen atom of the -NH group may be replaced by a C_{1-3}-alkyl, C_{1-3}-alkylcarbonyl, phenylcarbonyl or phenylsulphonyl group,

a C_{1-6}-alkylcarbonyl group optionally terminally substituted in the alkyl moiety by an amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group,

a group of formula $R_fR_gN\text{-}(CH_2)_m\text{-}(R_h)N\text{-}CO$ wherein
R_f, R_g and R_h independently of one another each denote a hydrogen atom or a C_{1-3}-alkyl group and
m denotes one of the numbers 2, 3, 4, 5 or 6,

a phenylcarbonyl, naphthylcarbonyl or heteroarylcarbonyl group,

a C_{1-3}-alkyl group monosubstituted by a hydroxy group or terminally disubstituted by a phenyl and a hydroxy group wherein

the phenyl substituent may be substituted by an amidino group optionally substituted by one or two C_{1-3}-alkyl groups, by a fluorine, chlorine or bromine atom, by a trifluoromethyl, C_{1-3}-alkyl or C_{1-3}-alkoxy group,

a 4- to 7-membered cycloalkyleneimino-carbonyl or cycloalkyleneimino-sulphonyl group substituted by an amino-C_{1-3}-alkyl, C_{1-3}-alkylamino-C_{1-3}-alkyl, di-(C_{1-3}-alkyl)-amino-C_{1-3}-alkyl, aminocarbonyl, C_{1-3}-alkylamino-carbonyl or di-(C_{1-3}-alkyl)-aminocarbonyl group,

a C_{3-7}-cycloalkylamino group which is substituted at the nitrogen atom by a C_{1-3}-alkyl-amino-C_{1-3}-alkyl or di-(C_{1-3}-alkyl)amino-C_{1-3}-alkyl group,

or, if R_5 denotes an amino-C_{1-3}-alkyl, C_{1-3}-alkylamino-C_{1-3}-alkyl or di-(C_{1-3}-alkyl)amino-C_{1-3}-alkyl group and/or at least one of the groups R_8 or R_9 denotes a C_{1-3}-alkyl group, an unsubstituted 4- to 7-membered cycloalkyleneimino-carbonyl or cycloalkyleneimino-sulphonyl group, a C_{3-7}-cycloalkylamino or N-(C_{1-3}-alkyl)-C_{3-7}-cycloalkylamino group,

R_2 denotes a hydrogen, fluorine, chlorine or bromine atom, a C_{1-3}-alkyl group wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, a hydroxy or C_{1-3}-alkoxy group,

R_3 denotes a hydrogen atom or a C_{1-3}-alkyl group,

R_4 denotes a hydrogen atom or a C_{1-3}-alkyl group optionally substituted by a carboxy group or a group which may be converted into a carboxy group in vivo,

Ar denotes a phenyl or naphthyl group substituted by the groups R_5, R_6 and R_7, while

R_5 denotes a cyano group, an amidino group optionally substituted by one or two C_{1-3}-alkyl groups, an amino-C_{1-3}-alkyl, C_{1-3}-alkylamino-C_{1-3}-alkyl or di-(C_{1-3}-alkyl)amino-C_{1-3}-alkyl group,

R_6 denotes a hydrogen, fluorine, chlorine or bromine atom, a trifluoromethyl, C_{1-3}-alkyl, hydroxy, hydroxy-C_{1-3}-alkyl, C_{1-3}-alkoxy, C_{1-3}-alkoxy-C_{1-3}-alkyl, carboxy, carboxy-C_{1-3}-alkyl, carboxy-C_{1-3}-alkoxy, C_{1-4}-alkoxy-carbonyl-C_{1-3}-alkoxy, phenyl-C_{1-3}-alkoxy, amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)amino group and

R_7 denotes a hydrogen, fluorine, chlorine or bromine atom or a C_{1-3}-alkyl group,

or a thienylene, thiazolylene, pyridinylene, pyrimidinylene, pyrazinylene or pyridazinylene group optionally substituted in the carbon skeleton by a C_{1-3}-alkyl group,

R_8 and R_9, which may be identical or different, each denote a hydrogen atom or a C_{1-3}-alkyl group,

while the term heteroaryl group mentioned above denotes a 5-membered heteroaryl group bound via a carbon or nitrogen atom which contains

an imino group optionally substituted by a C_{1-3}-alkyl group, an oxygen or sulphur atom,

an imino group optionally substituted by a C_{1-3}-alkyl group or an oxygen, sulphur or nitrogen atom,

an imino group optionally substituted by a C_{1-3}-alkyl group and two nitrogen atoms or

an oxygen or sulphur atom and two nitrogen atoms,

or a 6-membered heteroaryl group which contains one or two nitrogen atoms,

while a phenyl ring may be fused to the abovementioned 5- or 6-membered heteroaryl groups via two adjacent carbon atoms and the bicyclic heteroaryl groups thus formed may be bound via the heteroaromatic or carbocyclic moiety,

and the unsubstituted or monosubstituted phenyl and naphthyl groups mentioned in the definition of the abovementioned groups, or the unsubstituted or monosubstituted phenyl and naphthyl groups contained in these groups, as well as the abovementioned heteroaryl groups may additionally be substituted at a carbon atom in each case by a fluorine, chlorine or bromine atom, by a trifluoromethyl, C_{1-3}-alkyl or C_{1-3}-alkoxy group, unless otherwise stated.

The carboxy groups mentioned in the definition of the abovementioned groups may be replaced by a group which may be converted *in vivo* into a carboxy group or by a group which is negatively charged under physiological conditions,

and moreover the amino and imino groups mentioned in the definition of the abovementioned groups may be substituted by a group which can be cleaved *in vivo*. Such groups are described for example in WO 98/46576 and by N.M. Nielsen *et al.* in International Journal of Pharmaceutics 39, 75-85 (1987).

By a group which can be converted *in vivo* into a carboxy group is meant, for example, a hydroxymethyl group, a carboxy group esterified with an alcohol wherein the alcohol moiety is preferably a C_{1-6}-alkanol, a phenyl-C_{1-3}-alkanol, a C_{3-9}-cycloalkanol, while a C_{5-8}-cycloalkanol may additionally be substituted by one or two C_{1-3}-alkyl groups, a C_{5-8}-cycloalkanol wherein a methylene group in the 3 or 4 position is replaced by an oxygen atom or by an imino group optionally substituted by a C_{1-3}-alkyl, phenyl-C_{1-3}-alkyl, phenyl-C_{1-3}-alkoxycarbonyl or C_{2-6}-alkanoyl group and the cycloalkanol moiety may additionally be substituted by one or two C_{1-3}-alkyl groups, a C_{4-7}-cycloalkenol, a C_{3-5}-alkenol, a phenyl-C_{3-5}-alkenol, a C_{3-5}-alkynol or phenyl-C_{3-5}-alkynol with the proviso that no bonds to the oxygen atom start from a carbon atom which carries a double or triple bond, a C_{3-8}-cycloalkyl-C_{1-3}-alkanol, a bicycloalkanol with a total of 8 to 10 carbon atoms which may additionally be substituted in the bicycloalkyl moiety by one or two C_{1-3}-alkyl groups, a 1,3-dihydro-3-oxo-1-isobenzofuranol or an alcohol of formula

$$R_a\text{-CO-O-}(R_bCR_c)\text{-OH},$$

wherein

R_a denotes a C_{1-8}-alkyl, C_{5-7}-cycloalkyl, phenyl or phenyl-C_{1-3}-alkyl group,

R_b denotes a hydrogen atom, a C_{1-3}-alkyl, C_{5-7}-cycloalkyl or phenyl group and

R_c denotes a hydrogen atom or a C_{1-3}-alkyl group,

by a group which is negatively charged under physiological conditions is meant, for example, a tetrazol-5-yl, phenylcarbonylaminocarbonyl, trifluoromethylcarbonylaminocarbonyl, C_{1-6}-alkylsulphonylamino, phenylsulphonylamino, benzylsulphonylamino, trifluoromethylsulphonylamino, C_{1-6}-alkylsulphonylaminocarbonyl, phenylsulphonylaminocarbonyl, benzylsulphonylaminocarbonyl or perfluoro-C_{1-6}-alkylsulphonylaminocarbonyl group

and by a group which can be cleaved *in vivo* from an imino or amino group is meant, for example, a hydroxy group, an acyl group such as a phenylcarbonyl group optionally mono- or disubstituted by fluorine, chlorine, bromine or iodine atoms, by C_{1-3}-alkyl or C_{1-3}-alkoxy groups, while the substituents may be identical or different, , a pyridinoyl group or a C_{1-16}-alkanoyl group such as the formyl, acetyl, propionyl, butanoyl, pentanoyl or hexanoyl group, a 3,3,3-trichloropropionyl or allyloxycarbonyl group, a C_{1-16}-alkoxycarbonyl or C_{1-16}-alkylcarbonyloxy group, wherein hydrogen atoms may be wholly or partially replaced by fluorine or chlorine atoms such as the methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, tert.butoxycarbonyl, pentoxycarbonyl, hexoxycarbonyl, octyloxycarbonyl, nonyloxycarbonyl, decyloxycarbonyl, undecyloxycarbonyl, dodecyloxycarbonyl, hexadecyloxycarbonyl, methylcarbonyloxy, ethylcarbonyloxy, 2,2,2-trichloroethylcarbonyloxy, propylcarbonyloxy, isopropylcarbonyloxy, butylcarbonyloxy, tert.butylcarbonyloxy, pentylcarbonyloxy, hexylcarbonyloxy, octylcarbonyloxy, nonylcarbonyloxy, decylcarbonyloxy, undecylcarbonyloxy, dodecylcarbonyloxy or hexadecylcarbonyloxy group, a phenyl-C_{1-6}-alkoxycarbonyl group such as the benzyloxycarbonyl, phenylethoxycarbonyl or phenylpropoxycarbonyl group, a 3-amino-propionyl group wherein the amino group

may be mono- or disubstituted by C_{1-6}-alkyl or C_{3-7}-cycloalkyl groups and the substituents may be identical or different, a C_{1-3}-alkylsulphonyl-C_{2-4}-alkoxycarbonyl, C_{1-3}-alkoxy-C_{2-4}-alkoxy-C_{2-4}-alkoxycarbonyl, R_a-CO-O-(R_bCR_c)-O-CO, C_{1-6}-alkyl-CO-NH-(R_dCR_e)-O-CO or C_{1-6}-alkyl-CO-O-(R_dCR_e)-(R_dCR_e)-O-CO- group, wherein R_a to R_c are as hereinbefore defined,

R_d and R_e, which may be identical or different, denote hydrogen atoms or C_{1-3}-alkyl groups.

Moreover, the saturated alkyl and alkoxy moieties containing more than 2 carbon atoms mentioned in the definitions above also include the branched isomers thereof such as the isopropyl, tert.butyl, isobutyl group, etc.

Preferred compounds of the above general formula I are those wherein

R_1 denotes a C_{5-7}-cycloalkyl-carbonyl group wherein the methylene group in the 3 or 4 position is replaced by an -NH group wherein

the hydrogen atom may be replaced by a C_{1-3}-alkyl, C_{1-3}-alkyl-carbonyl or phenylcarbonyl group,

a C_{1-3}-alkyl-carbonyl group optionally terminally substituted in the alkyl moiety by a C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group,

a group of formula R_fR_gN-$(CH_2)_m$-(R_h)N-CO, wherein

R_f, R_g and R_h independently of one another each denote a hydrogen atom or a C_{1-3}-alkyl group and
m denotes one of the numbers 2, 3 or 4,

a phenylcarbonyl or heteroarylcarbonyl group,

while the heteroaryl moiety contains a 6-membered heteroaryl group which contains one or two nitrogen atoms and to which a phenyl ring may be fused via two adjacent carbon atoms, while the bicyclic heteroaryl groups thus formed may be bound via the heteroaromatic or carbocyclic moiety, e.g. a 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinolinyl, isoquinolinyl, quinoxalinyl or quinazolinyl group,

a C_{1-3}-alkyl group monosubstituted by a hydroxy group or terminally disubstituted by a phenyl group and a hydroxy group wherein

the phenyl substituent may be substituted by an amidino group optionally substituted by one or two C_{1-3}-alkyl groups, by a fluorine, chlorine or bromine atom, by a trifluoromethyl, C_{1-3}-alkyl or C_{1-3}-alkoxy group,

a 4- to 7-membered cycloalkyleneimino-carbonyl group substituted by an amino-C_{1-3}-alkyl, C_{1-3}-alkylamino-C_{1-3}-alkyl, di-(C_{1-3}-alkyl)-amino-C_{1-3}-alkyl, C_{1-4}-alkoxy-carbonyl-amino-C_{1-3}-alkyl, aminocarbonyl, C_{1-3}-alkylamino-carbonyl or di-(C_{1-3}-alkyl)-aminocarbonyl group,

a C_{5-7}-cycloalkylamino group which is substituted at the nitrogen atom by a C_{1-3}-alkyl-amino-C_{1-3}-alkyl or di-(C_{1-3}-alkyl)amino-C_{1-3}-alkyl group,

or, if R_5 denotes an amino-C_{1-3}-alkyl or C_{1-3}-alkylamino-C_{1-3}-alkyl group and/or at least one of the groups R_8 or R_9 denotes a C_{1-3}-alkyl group, an unsubstituted 4- to 7-membered cycloalkyleneiminocarbonyl group, a C_{5-7}-cycloalkylamino or N-(C_{1-3}-alkyl)-C_{5-7}-cycloalkylamino group,

R_2 denotes a hydrogen, fluorine, chlorine or bromine atom, a C_{1-3}-alkyl, trifluoromethyl or C_{1-3}-alkoxy group,

R_3 denotes a hydrogen atom or a C_{1-3}-alkyl group,

R_4 denotes a hydrogen atom or a C_{1-3}-alkyl group,

Ar denotes a phenyl group substituted by the groups R_5 and R_6 wherein

R_5 denotes a cyano group, an amidino group optionally substituted by one or two C_{1-3}-alkyl groups, an amino-C_{1-3}-alkyl or C_{1-3}-alkylamino-C_{1-3}-alkyl group and

R_6 denotes a hydrogen, fluorine, chlorine or bromine atom, a trifluoromethyl, C_{1-3}-alkyl, hydroxy, C_{1-3}-alkoxy, carboxy-C_{1-3}-alkoxy or C_{1-4}-alkoxy-carbonyl-C_{1-3}-alkoxy group, and

R_8 and R_9, which may be identical or different, each denote a hydrogen atom or a C_{1-3}-alkyl group,

while the unsubstituted or monosubstituted phenyl groups mentioned in the definition of the abovementioned groups, or the unsubstituted or monosubstituted phenyl moieties contained in these groups, as well as the abovementioned heteroaryl groups may additionally be substituted at a carbon atom in each case by a fluorine, chlorine or bromine atom, by a trifluoromethyl, C_{1-3}-alkyl or C_{1-3}-alkoxy group, unless otherwise stated,

and the compound

2-(5-carbamimidoyl-2-hydroxy-phenyl)-N-[3-chloro-4-(pyrrolidin-1-yl-carbonyl)-phenyl]-acetamide,

the isomers and the salts thereof,

but particularly those compounds wherein

the groups R_1 to R_4, R_8 and R_9 are as hereinbefore defined, but R_1 in the 4 position is bound to the phenyl group contained in formula I and

Ar denotes a phenyl group disubstituted by the groups R_5 and R_6, while

R_5 is bound in the 3 position if R_6 denotes a hydrogen atom, or is bound in the 5 position if R_6 assumes a meaning other than the hydrogen atom, and an amidino group optionally substituted by one or two C_{1-3}-alkyl groups, an amino-C_{1-3}-alkyl or C_{1-3}-alkylamino-C_{1-3}-alkyl group and

R_6 denotes a hydrogen atom or a trifluoromethyl, C_{1-3}-alkyl, hydroxy, C_{1-3}-alkoxy, carboxy-C_{1-3}-alkoxy or C_{1-4}-alkoxy-carbonyl-C_{1-3}-alkoxy group bound in the 2 position,

the isomers and the salts thereof.

Particularly preferred compounds of general formula I are those wherein

R_1 is bound in the 4 position of the phenyl group of formula I and denotes

a C_{5-7}-cycloalkyl-carbonyl group wherein the methylene group in the 3 or 4 position is replaced by an -NH group,

a phenylcarbonyl group optionally substituted by a fluorine, chlorine or bromine atom or by a C_{1-3}-alkyl group,

a C_{1-3}-alkyl group terminally disubstituted by a phenyl and a hydroxy group wherein

the phenyl substituent may be monosubstituted by a C_{1-3}-alkyl or an amidino group or may be disubstituted by a C_{1-3}-alkyl and an amidino group,

a 5- to 7-membered cycloalkyleneimino-carbonyl group substituted by an amino-C_{1-3}-alkyl, C_{1-3}-alkylamino-C_{1-3}-alkyl, C_{1-4}-alkoxy-carbonyl-amino-C_{1-3}-alkyl, aminocarbonyl or C_{1-3}-alkylamino-carbonyl group,

or, if R_5 denotes an amino-C_{1-3}-alkyl group and/or at least one of the groups R_8 or R_9 denotes a C_{1-3}-alkyl group, an unsubstituted 5- to 7-membered cycloalkyleneimino-carbonyl group and

R_2 denotes a hydrogen atom or a substitutent bound in the 3 position of the phenyl group, selected from among fluorine, chlorine, bromine, C_{1-3}-alkyl and trifluoromethyl,

R_3 and R_4 each denote a hydrogen atom,

Ar denotes a phenyl group substituted by the groups R_5 and R_6 wherein

R_5 is bound in the 3 position if R_6 denotes a hydrogen atom, or is bound in the 5 position if R_6 assumes a meaning other than the hydrogen atom, and an amidino or amino-C_{1-3}-alkyl group and

R_6 denotes a hydrogen atom or a hydroxy, C_{1-3}-alkoxy, carboxy-C_{1-3}-alkoxy or C_{1-4}-alkoxy-carbonyl-C_{1-3}-alkoxy group bound in the 2 position, and

R_8 and R_9, which may be identical or different, each denote a hydrogen atom or a C_{1-3}-alkyl group,

the isomers and the salts thereof.

The following preferred compounds are mentioned by way of example:

(1) (L)-2-(5-carbamimidoyl-2-hydroxy-phenyl)-N-[3-methyl-4-(2-aminocarbonyl-pyrrolidin-1-yl-carbonyl)-phenyl]-acetamide,

(2) 2-(5-carbamimidoyl-2-hydroxy-phenyl)-N-[3-methyl-4-(2-tert.butoxycarbonylaminomethyl-piperidin-1-yl-carbonyl)-phenyl]-acetamide,

(3) 2-(5-aminomethyl-2-hydroxy-phenyl)-N-[3-methyl-4-(pyrrolidin-1-yl-carbonyl)-phenyl]-acetamide,

(4) 2-(3-carbamimidoyl-phenyl)-N-[3-methyl-4-(pyrrolidin-1-yl-carbonyl)-phenyl]-2,2-dimethylacetamide,

(5) 2-(5-carbamimidoyl-2-ethoxycarbonylmethyloxy-phenyl)-N-[3-methyl-4-(pyrrolidin-1-yl-carbonyl)-phenyl]-acetamide,

(6) 2-(5-carbamimidoyl-2-carboxymethyloxy-phenyl)-N-[3-methyl-4-(pyrrolidin-1-yl-carbonyl)-phenyl]-acetamide,

(7) 2-(5-carbamimidoyl-2-hydroxy-phenyl)-N-[3-methyl-4-(piperidin-3-yl-carbonyl)-phenyl]-acetamide,

(8) 2-(5-carbamimidoyl-2-hydroxy-phenyl)-N-(3-methyl-4-benzoyl-phenyl)-acetamide,

(9) 2-(5-carbamimidoyl-2-hydroxy-phenyl)-N-[3-methyl-4-(hydroxy-phenyl-methyl)-phenyl]-acetamide,

(10) 2-(5-carbamimidoyl-2-hydroxy-phenyl)-N-{4-[(3-carbamimidoyl-phenyl)-hydroxy-methyl]-3-methyl-phenyl}-acetamide,

(11) 2-(5-carbamimidoyl-2-hydroxy-phenyl)-N-[3-methyl-4-(pyrrolidin-1-yl-carbonyl)-phenyl]-2,2-dimethylacetamide and

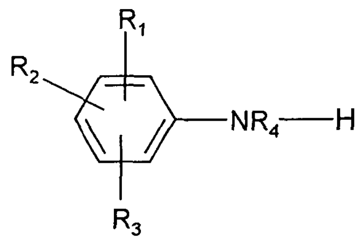
(12) 2-(5-carbamimidoyl-2-hydroxy-phenyl)-N-[3-chloro-4-(pyrrolidin-1-yl-carbonyl)-phenyl]-acetamide,

wherein the amidino group may additionally be substituted by a C_{1-6}-alkoxycarbonyl or phenylcarbonyl group, and the salts thereof.

According to the invention, the compounds of general formula I are obtained by methods known *per se*, e.g. by the following processes:

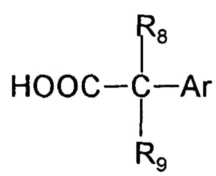
a) In order to prepare a compound of general formula I wherein Ar denotes a phenyl or naphthyl group substituted by the groups R_5, R_6 and R_7, while R_6 and R_7 are as hereinbefore defined and R_5 denotes an amidino group:

acylating a compound of general formula



(II),

wherein R_1 to R_4 are as hereinbefore defined, with a carboxylic acid of general formula



(III),

wherein R_8 and R_9 are as hereinbefore defined and Ar denotes a phenyl or naphthyl group substituted by the groups R_5, R_6 and R_7, while R_5 denotes a cyano group and R_6 and R_7 are as hereinbefore defined, or with the reactive derivatives thereof and subsequently converting the cyano compound thus obtained into an amidino compound.

The acylation is conveniently carried out with a corresponding halide or anhydride in a solvent such as methylene chloride, chloroform, carbon tetrachloride, ether, tetrahydrofuran, dioxan, benzene, toluene, acetonitrile or sulpholane optionally in the presence of an inorganic or organic base at temperatures between -20 and 200°C, but preferably at temperatures between -10 and 160°C.

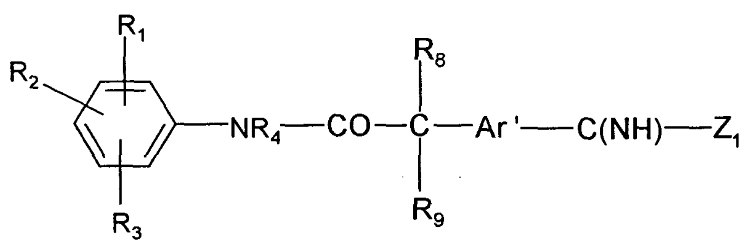
The acylation may however also be carried out with the free acid, optionally in the presence of an acid-activating agent or a dehydrating agent, e.g. in the presence of isobutyl chloroformate, thionyl chloride, trimethylchlorosilane, hydrogen chloride, sulphuric acid, methanesulphonic acid, p-toluenesulphonic acid, phosphorus

trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide or 1-hydroxy- benzotriazole, N,N'-carbonyldiimidazole or N,N'-thionyldiimidazole or triphenylphosphine/carbon tetrachloride, at temperatures between -20 and 200°C, but preferably at temperatures between -10 and 160°C.

The subsequent conversion of the cyano group into an amidino group takes place as described in process b).

b) In order to prepare a compound of general formula I wherein Ar denotes a phenyl or naphthyl group substituted by the groups R_5, R_6 and R_7, while R_6 and R_7 are as hereinbefore defined and R_5 denotes an amidino group optionally substituted by one or two C_{1-3}-alkyl groups:

reacting a compound of general formula



(IV),

optionally formed in the reaction mixture, wherein

R_1 to R_4, R_8 and R_9 are as hereinbefore defined, Ar' denotes a phenyl or naphthyl group substituted by the groups R_6 and R_7, while R_6 and R_7 are as hereinbefore defined, and

Z_1 denotes an alkoxy or aralkoxy group such as the methoxy, ethoxy, n-propoxy, iso-propoxy or benzyloxy group or an alkylthio or aralkylthio group such as the methylthio, ethylthio, n-propylthio or benzylthio group, with an amine of general formula

$$H - R_{10}NR_{11} \text{ , (V)}$$

wherein

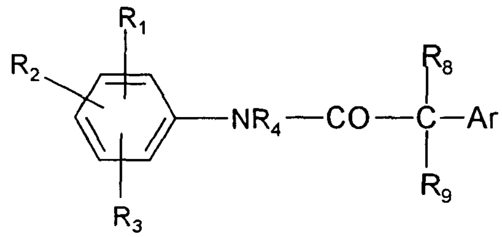
R_{10} and R_{11}, which may be identical or different, each denote a hydrogen atom or a C_{1-3}-alkyl group, or with the salts thereof.

The reaction is conveniently carried out in a solvent such as methanol, ethanol, n-propanol, tetrahydrofuran or dioxan at temperatures between 0 and 150°C, preferably at temperatures between 0 and 80°C, with an amine of general formula V or with a corresponding acid addition salt such as for example ammonium carbonate or ammonium acetate.

A compound of general formula IV is obtained for example by reacting a corresponding cyano compound with a corresponding alcohol such as methanol, ethanol, n-propanol, isopropanol or benzyl alcohol in the presence of an acid such as hydrochloric acid or by reacting a corresponding amide with a trialkyloxonium salt such as triethyloxonium-tetrafluoroborate in a solvent such as methylene chloride, tetrahydrofuran or dioxan at temperatures between 0 and 50°C, but preferably at 20°C, or a corresponding nitrile with hydrogen sulphide conveniently in a solvent such as pyridine or dimethylformamide and in the presence of a base such as triethylamine and subsequently alkylating the thioamide formed with a corresponding alkyl or aralkyl halide.

c) In order to prepare a compound of general formula I wherein Ar denotes a phenyl or naphthyl group substituted by the groups R_5, R_6 and R_7, while R_6 and R_7 are as hereinbefore defined and R_5 denotes an aminomethyl, C_{1-3}-alkylaminomethyl or di-(C_{1-3}-alkyl)aminomethyl group:

Catalytic hydrogenation of a compound of general formula



(I'),

wherein

Ar denotes a phenyl or naphthyl group substituted by the groups R_5, R_6 and R_7, R_1 to R_4 and R_6 to R_9 are as hereinbefore defined and R_5 denotes a cyano group, and optionally subsequent alkylation with a compound of formula

$$R_{12} - Z_2 \qquad \text{(VI)},$$

wherein R_{12} denotes a C_{1-3}-alkyl group and Z_2 denotes a leaving group such as a halogen atom or a sulphonyloxy group, e.g. a chlorine, bromine or iodine atom or a trifluoromethylsulphonyloxy group.

The catalytic hydrogenation is carried out with hydrogen in the presence of a catalyst such as palladium/charcoal, platinum in a solvent such as methanol, ethanol, ethyl acetate, dimethylformamide, dimethylformamide/acetone or glacial acetic acid optionally with the addition of an acid such as hydrochloric acid at temperatures between 0 and 50°C, but preferably at ambient temperature, and at a hydrogen pressure of 1 to 7 bar, but preferably 3 to 5 bar, or for example with Raney nickel preferably in methanolic ammonia solution.

The alkylation which optionally follows is conveniently carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran, dioxan, dimethylsulphoxide or sulpholane with an alkylating agent such as a corresponding halide or sulphonic acid ester, e.g. with methyl iodide, ethyl bromide, dimethylsulphate or benzyl chloride, optionally in the presence of a tertiary organic base or in the presence of an inorganic base conveniently at temperatures between 0 and 150°C, preferably at temperatures between 0 and 100°C.

If according to the invention a compound of general formula I is obtained which contains an amino or imino group, this may subsequently be converted with a corresponding acyl derivative into a corresponding acyl compound of general formula I and/or

if a compound of general formula I is obtained which contains an esterified carboxy group, this may be converted by hydrolysis into a corresponding carboxylic acid of general formula I and/or

if a compound of general formula I is obtained which contains a carboxy group, this may subsequently be converted by esterification into a corresponding ester.

The subsequent acylation is conveniently carried out with a corresponding halide or anhydride in a solvent such as methylene chloride, chloroform, carbon tetrachloride, ether, tetrahydrofuran, dioxan, benzene, toluene, acetonitrile or sulpholane optionally in the presence of an inorganic or organic base at temperatures between -20 and 200°C, but preferably at temperatures between -10 and 160°C. This may however also be carried out with the free acid, optionally in the presence of an acid-activating agent or a dehydrating agent, e.g. in the presence of isobutyl chloroformate, thionyl chloride, trimethylchlorosilane, hydrogen chloride, sulphuric acid, methanesulphonic acid, p-toluenesulphonic acid, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide or 1-hydroxy-benzotriazole, N,N'-carbonyldiimidazole or N,N'-thionyldiimidazole or triphenylphosphine/carbon tetrachloride, at temperatures between -20 and 200°C, but preferably at temperatures between -10 and 160°C.

The subsequent hydrolysis is conveniently carried out either in the presence of an acid such as hydrochloric acid, sulphuric acid, phosphoric acid, acetic acid, trichloroacetic acid, trifluoroacetic acid or mixtures thereof or in the presence of a base such as lithium hydroxide, sodium hydroxide or potassium hydroxide in a suitable solvent such as water, water/methanol, water/ethanol, water/isopropanol, methanol, ethanol, water/tetrahydrofuran or water/dioxan and the subsequent decarboxylation in the presence of an acid as hereinbefore described at

temperatures between -10 and 120°C, e.g. at temperatures between ambient temperature and the boiling temperature of the reaction mixture.
The subsequent esterification is carried out with a corresponding alcohol, conveniently in a solvent or mixture of solvents such as methylene chloride, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxan, but preferably in an excess of the alcohol used, optionally in the presence of an acid such as hydrochloric acid or in the presence of a dehydrating agent, e.g. in the presence of isobutyl chloroformate, thionyl chloride, trimethylchlorosilane, hydrochloric acid, sulphuric acid, methanesulphonic acid, p-toluenesulphonic acid, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide, N,N'-carbonyldiimidazole or N,N'-thionyldiimidazole, triphenylphosphine/carbon tetrachloride or triphenyl-phosphine/diethyl azodicarboxylate, optionally in the presence of a base such as potassium carbonate, N-ethyl-diisopropylamine or N,N-dimethylamino-pyridine, conveniently at temperatures between 0 and 150°C, preferably at temperatures between 0 and 80°C, or with a corresponding halide in a solvent such as methylene chloride, tetrahydrofuran, dioxan, dimethylsulphoxide, dimethylformamide or acetone optionally in the presence of a reaction accelerator such as sodium or potassium iodide and preferably in the presence of a base such as sodium carbonate or potassium carbonate or in the presence of a tertiary organic base such as N-ethyl-diisopropylamine or N-methyl-morpholine, which may also simultaneously serve as the solvent, or optionally in the presence of silver carbonate or silver oxide at temperatures between -30 and 100°C, but preferably at temperatures between -10 and 80°C.

In the reactions described hereinbefore, any reactive groups present such as hydroxy, carboxy, amino, alkylamino or imino groups may be protected during the reaction by conventional protecting groups which are cleaved again after the reaction.

For example, a protecting group for a hydroxy group may be a methoxy, benzyloxy, trimethylsilyl, acetyl, benzoyl, tert-butyl, trityl, benzyl or tetrahydropyranyl group,

protecting groups for a carboxy group may be a trimethylsilyl, methyl, ethyl, tert.butyl, benzyl or tetrahydropyranyl group and

protecting groups for an amino, alkylamino or imino group may be an acetyl, trifluoroacetyl, benzoyl, ethoxycarbonyl, tert-butoxycarbonyl, benzyloxycarbonyl, benzyl, methoxybenzyl or 2,4-dimethoxybenzyl group and additionally, for the amino group, a phthalyl group.

Any protecting group used is optionally subsequently cleaved for example by hydrolysis in an aqueous solvent, e.g. in water, isopropanol/water, tetrahydrofuran/water or dioxan/water, in the presence of an acid such as trifluoroacetic acid, hydrochloric acid or sulphuric acid or in the presence of an alkali metal base such as lithium hydroxide, sodium hydroxide or potassium hydroxide or by ether splitting, e.g. in the presence of iodotrimethylsilane, at temperatures between 0 and 100°C, preferably at temperatures between 10 and 50°C.

However, a benzyl, methoxybenzyl or benzyloxycarbonyl group is cleaved, for example, hydrogenolytically, e.g. with hydrogen in the presence of a catalyst such as palladium/charcoal in a solvent such as methanol, ethanol, ethyl acetate, dimethylformamide, dimethylformamide/acetone or glacial acetic acid optionally with the addition of an acid such as hydrochloric acid at temperatures between 0 and 50°C, but preferably at ambient temperature, and at a hydrogen pressure of 1 to 7 bar, but preferably 3 to 5 bar.

A methoxybenzyl group may also be cleaved in the presence of a oxidising agent such as cerium(IV)ammonium nitrate in a solvent such as methylene chloride, acetonitrile or acetonitrile/water at temperatures between 0 and 50°C, but preferably at ambient temperature.

A methoxy group is conveniently cleaved in the presence of boron tribromide in a solvent such as methylene chloride at temperatures between -35 and -25°C.

A 2,4-dimethoxybenzyl group, however, is preferably cleaved in trifluoroacetic acid in the presence of anisole.

A tert.butyl or tert.butyloxycarbonyl group is preferably cleaved by treating with an acid such as trifluoroacetic acid or hydrochloric acid, optionally using a solvent such as methylene chloride, dioxan or ether.

A phthalyl group is preferably cleaved in the presence of hydrazine or a primary amine such as methylamine, ethylamine or n-butylamine in a solvent such as methanol, ethanol, isopropanol, toluene/water or dioxan at temperatures between 20 and 50°C.

An allyloxycarbonyl group is cleaved by treating with a catalytic amount of tetrakis-(triphenylphosphine)-palladium(O), preferably in a solvent such as tetrahydrofuran and preferably in the presence of an excess of a base such as morpholine or 1,3-dimedone at temperatures between 0 and 100°C, preferably at ambient temperature and under inert gas, or by treating with a catalytic amount of tris-(triphenylphosphine)-rhodium(I)chloride in a solvent such as aqueous ethanol and optionally in the presence of a base such as 1,4-diazabicyclo[2.2.2]octane at temperatures between 20 and 70°C.

The compounds of general formulae II to VI, used as starting materials, some of which are known from the literature, are obtained by methods known from the literature and their preparation is also described in the Examples.

The chemistry of the compounds of general formula II is described, for example, by Schröter in Stickstoffverbindungen II, pages 341-730, Methoden der organischen Chemie (Houben-Weyl), 4th edition, Verlag Thieme, Stuttgart 1957. The preparation of carboxylic acid derivatives of general formula III is described in Methoden der organischen Chemie (Houben-Weyl), Volume E5, Carbonsäuren und Carbonsäurederivate, 4th edition, Verlag Thieme, Stuttgart 1985.

Moreover, the compounds of general formula I obtained may be resolved into their enantiomers and/or diastereomers.

Thus, for example, the compounds of general formula I obtained which occur as racemates may be separated by methods known per se (cf. Allinger N. L. and Eliel E. L. in "Topics in Stereochemistry", Vol. 6, Wiley Interscience, 1971) into their optical enantiomers and compounds of general formula I with at least 2 asymmetric carbon atoms may be resolved into their diastereomers on the basis of their physical-chemical differences using methods known per se, e.g. by chromatography and/or fractional crystallisation, and, if these compounds are obtained in racemic form, they may subsequently be resolved into the enantiomers as mentioned above.

The enantiomers are preferably separated by column separation on chiral phases or by recrystallisation from an optically active solvent or by reacting with an optically active substance which forms salts or derivatives such as e.g. esters or amides with the racemic compound, particularly acids and the activated derivatives or alcohols thereof, and separating the diastereomeric mixture of salts or derivatives thus obtained, e.g. on the basis of their differences in solubility, whilst the free antipodes may be released from the pure diastereomeric salts or derivatives by the action of suitable agents. Optically active acids in common use are e.g. the D- and L-forms of tartaric acid or dibenzoyltartaric acid, di-o-tolyltartaric acid, malic acid, mandelic acid, camphorsulphonic acid, glutamic acid, aspartic acid or quinic acid. An optically active alcohol may be for example (+) or (-)-menthol and an optically active acyl group in amides, for example, may be a (+)- or (-)-menthyloxycarbonyl.

Furthermore, the compounds of formula I may be converted into the salts thereof, particularly for pharmaceutical use into the physiologically acceptable salts with inorganic or organic acids. Acids which may be used for this purpose include for example hydrochloric acid, hydrobromic acid, sulphuric acid, methanesulphonic acid, phosphoric acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid or maleic acid.

Moreover, if the new compounds of formula I contain a carboxy group, they may subsequently, if desired, be converted into the salts thereof with inorganic or organic bases, particularly for pharmaceutical use into the physiologically acceptable salts thereof. Suitable bases for this purpose include for example sodium hydroxide, potassium hydroxide, cyclohexylamine, ethanolamine, diethanolamine and triethanolamine.

As already mentioned, the new compounds of general formula I and the compound 2-(5-carbamimidoyl-2-hydroxy-phenyl)-N-[3-chloro-4-(pyrrolidin-1-yl-carbonyl)-phenyl]-acetamide and the salts thereof have valuable properties. Thus, the compounds of general formula I wherein Ar denotes a phenyl or naphthyl group substituted by the groups R_5, R_6 and R_7, and R_5 denotes a cyano group, are valuable intermediates for preparing the corresponding compounds of general formula I wherein R_5 denotes an amidino group optionally substituted by one or two C_{1-3}-alkyl groups. The compounds of general formula I with the exception of those compounds wherein Ar denotes a phenyl or naphthyl group substituted by the groups R_5, R_6 and R_7, and R_5 denotes a cyano group, as well as the tautomers, the stereoisomers and the physiologically acceptable salts thereof, have valuable pharmacological properties, particularly an antithrombotic activity which is preferably based on an effect on thrombin or factor Xa, e.g. on an inhibitory effect on thrombin or factor Xa, on a prolonging effect on aPTT time and on an inhibitory effect on related serine proteases such as e.g. trypsin, urokinase, factor VIIa, factor IX, factor XI and factor XII.

For example, the compounds

(1) 2-(3-carbamimidoyl-phenyl)-N-[3-methyl-4-(pyrrolidin-1-yl-carbonyl)-phenyl]-2,2-dimethylacetamide-hydrochloride,

(2) 2-(5-carbamimidoyl-2-hydroxy-phenyl)-N-[3-methyl-4-(piperidin-3-yl-carbonyl)-phenyl]-acetamide and

(3) 2-(5-carbamimidoyl-2-hydroxy-phenyl)-N-[3-chloro-4-(pyrrolidin-1-yl-carbonyl)-phenyl]-acetamide-hydrochloride

were investigated for their effect on the inhibition of factor Xa as follows:

Method: Enzyme-kinetic measurement with chromogenic substrate. The quantity of anp-nitroaniline (pNA) released from the colourless chromogenic substrate by human factor Xa is determined photometrically at 405 nm. It is proportional to the activity of the enzyme used. The inhibition of the enzyme activity by the test substance (in relation to the solvent control) is determined at various concentrations of test substance and from this the IC_{50} is calculated, as the concentration which inhibits the factor Xa used by 50 %.

Material:

Tris(hydroxymethyl)-aminomethane buffer (100 mmol) and sodium chloride (150 mMol), pH 8.0

Factor Xa (Roche), spec. activity: 10 U/0.5 ml, final concentration: 0.175 U/ml per reaction mixture

Substrate Chromozym X (Roche), final concentration: 200 μMol/l per reaction mixture

Test substance: final concentration 100, 30, 10, 3, 1, 0.3, 0.1, 0.03, 0.01, 0.003, 0.001 μMol/l

Procedure:

10 μl of a 23.5-times concentrated starting solution of the test substance or solvent (control), 175 μl of tris(hydroxymethyl)-aminomethane buffer and 25 μl of a 1.65 U/ml Factor Xa working solution are incubated for 10 minutes at 37°C. After the addition of 25 μl of Chromozym X working solution (1.88 μMol/l) the sample is measured in a photometer (SpectraMax 250) at 405 nm for 150 seconds at 37°C.

Evaluation:

1. Determining the maximum increase (deltaOD/minutes) over 3 measuring points.

2. Determining the % inhibition based on the solvent control.

3. Plotting a dosage/activity curve (% inhibition vs substance concentration).

4. Determining the IC_{50} by interpolating the X value (substance concentration) of the dosage/activity curve at Y = 50 % inhibition.

The following Table shows the results obtained:

Substance	Inhibition of factor Xa (IC_{50} in μM)
(1)	0.028
(2)	0.320
(3)	0.033

The compounds prepared according to the invention are well tolerated, as no toxic side effects could be observed at therapeutic doses.

In view of their pharmacological properties the new compounds, with the exception of those compounds wherein Ar denotes a phenyl or naphthyl group substituted by the groups R_5, R_6 and R_7, and R_5 denotes a cyano group, and the physiologically acceptable salts thereof are suitable for the prevention and treatment of venous and arterial thrombotic diseases, such as for example the treatment of deep leg vein thrombosis, for preventing reocclusions after bypass operations or angioplasty (PT(C)A), and occlusion in peripheral arterial diseases such as pulmonary embolism, disseminated intravascular coagulation, for preventing coronary thrombosis, stroke and the occlusion of shunts. In addition, the compounds according to the invention are suitable for antithrombotic support in thrombolytic treatment, such as for example with alteplase, reteplase, tenecteplase, staphylokinase or streptokinase, for preventing long-term restenosis after PT(C)A, for the prevention and treatment of ischaemic incidents in patients with unstable angina or non-transmural cardiac

infarct, for preventing metastasis and the growth of clot-dependent tumours and fibrin-dependent inflammatory processes, e.g. in the treatment of pulmonary fibrosis. The new compounds and the physiologically acceptable salts thereof may be used therapeutically in conjunction with inhibitors of platelet aggregation such as fibrinogen receptor antagonists (e.g. abciximab, eptifibatide, tirofiban), with inhibitors of ADP-induced aggregation (e.g. clopidogrel, ticlopidine), with P_2T receptor antagonists (e.g. cangrelor) or with combined thromboxane receptor antagonists/synthetase inhibitors (e.g. terbogrel).

The dosage required to achieve such an effect is appropriately 3 to 30 mg/kg, preferably 1 to 10 mg/kg by intravenous route, and 5 to 50 mg/kg, preferably 3 to 30 mg/kg by oral route, in each case administered 1 to 4 times a day. For this purpose, the compounds of formula I prepared according to the invention may be formulated, optionally together with other active substances, with one or more inert conventional carriers and/or diluents, e.g. with corn starch, lactose, glucose, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethylene glycol, propylene glycol, cetylstearyl alcohol, carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof, to produce conventional galenic preparations such as plain or coated tablets, capsules, powders, suspensions or suppositories.

The Examples which follow are intended to illustrate the invention:

Example 1

(L)-2-(5-carbamimidoyl-2-hydroxy-phenyl)-N-[3-methyl-4-(2-aminocarbonyl-pyrrolidin-1-yl-carbonyl)-phenyl]-acetamide-hydrochloride

a. 4-Allyloxy-benzonitrile

100.1 g (0.84 mol) of 4-hydroxy-benzonitrile are dissolved in 600 ml dimethylformamide and after the addition of 103.2 g (0.92 mol) of potassium tert. butoxide stirred for 30 minutes at 35°C. Then a solution of 79.6 ml (0.92 mol) of 3-bromopropene in 10 ml of dimethylformamide is added dropwise. After 1 hour at 60°C the reaction solution is poured onto ice water, combined with 300 ml of 2 molar sodium hydroxide solution and extracted with ethyl acetate. The organic extracts are dried and evaporated down.

Yield: 130.1 g (97 % of theoretical),

R_f value: 0.25 (silica gel; petroleum ether/ethyl acetate = 8:2)

b. 3-Allyl-4-hydroxy-benzonitrile

47.8 g (0.3 mol) of 4-allyloxy-benzonitrile are heated to 210°C under a nitrogen atmosphere for 60 minutes. After cooling the residue is chromatographed on silica gel, eluting with petroleum ether/ethyl acetate (9:1 and 1:1).

Yield: 14.7 g (31 % of theoretical),

R_f value: 0.45 (silica gel; petroleum ether/ethyl acetate = 1:1)

c. 3-Allyl-4-benzyloxy-benzonitrile

14.6 g (0.09 mol) of 3-allyl-4-hydroxy-benzonitrile and 34.6 g (0.25 mol) of potassium carbonate are stirred for 15 minutes in 200 ml dimethylformamide. After the addition of 12.1 ml (0.1 mol) of benzylbromide the reaction mixture is stirred for 2 hours at ambient temperature. The reaction solution is poured onto ice water and the crystalline product is suction filtered.

Yield: 19.9 g (87 % of theoretical),

R_f value: 0.55 (silica gel; petroleum ether/ethyl acetate = 8:2)

d. (2-benzyloxy-5-cyano)-phenylacetic acid

5.0 g (20 mmol) of 3-allyl-4-benzyloxy-benzonitrile are added in batches to a solution of 17.4 g (110 mmol) of potassium permanganate in 50 ml of water and 150 ml of glacial acetic acid, while the temperature rises to 55°C. After 1 hour at 40°C the reaction mixture is diluted with ethyl acetate and suction filtered through Celite. The organic phase is separated off and evaporated down. The residue is chromatographed on silica gel, eluting with petroleum ether/ethyl acetate (9:1 and 1:1).

Yield: 2.2 g (40 % of theoretical),

R_f value: 0.2 (silica gel; petroleum ether/ethyl acetate = 1:1)

e. tert.butyl 4-benzylamino-2-methyl-benzoate

21.5 g (77 mmol) of tert.butyl 4-bromo-2-methyl-benzoate and 10.2 g (93.2 mmol) of benzylamine are dissolved in 250 ml of toluene and after the addition of 38 g (116.6 mmol) of caesium carbonate, 1.8 g (7.8 mmol) of palladium-II-acetate and 4.9 g (7.8 mmol) of 2,2'-bis-(diphenylphosphino)-1,1'-binaphthyl heated to 100°C for 23 hours under a nitrogen atmosphere. After cooling the solution is filtered and evaporated down. The residue is chromatographed on silica gel, eluting with petroleum ether/ethyl acetate (95:5).

Yield: 16.7 g (72 % of theoretical),

R_f value: 0.3 (silica gel; petroleum ether/ethyl acetate = 9:1)

f. tert.butyl 4-amino-2-methyl-benzoate

13.5 g (45 mmol) of tert.butyl 4-benzylamino-2-methyl-benzoate are dissolved in 250 ml ethanol and after the addition of 5 g of palladium on activated charcoal (10%) hydrogenated with hydrogen for 45 minutes at ambient temperature. Then the catalyst is filtered off and the filtrate is evaporated down. The residue is triturated with petroleum ether and suction filtered.

Yield: 9.2 g (97 % of theoretical),

R_f value: 0.4 (silica gel; petroleum ether/ethyl acetate = 7:3)

g. 2-(5-Cyano-2-benzyloxy-phenyl)-N-(3-methyl-4-tert.butoxycarbonyl-phenyl)-acetamide

7.5 g (28 mmol) of (2-benzyloxy-5-cyano)-phenylacetic acid are dissolved in 200 ml of tetrahydrofuran and 20 ml dimethylformamide and after the addition of 9.5 g (29 mmol) of O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate, 3.4 ml (30.6 mmol) of N-methylmorpholine and 6.1 g (29.5 mmol) of tert.butyl 4-amino-2-methyl-benzoate stirred for 7 hours at 40°C.The solvent is distilled off, the residue is dissolved in ethyl acetate and combined with petroleum ether. The product precipitated is suction filtered and dried.

Yield: 8.5 g (66 % of theoretical),

R_f value: 0.33 (silica gel; petroleum ether/ethyl acetate = 7:3)

h. 2-(5-Cyano-2-benzyloxy-phenyl)-N-(3-methyl-4-carboxy-phenyl)-acetamide

4.4 g (9.6 mmol) of 2-(5-cyano-2-benzyloxy-phenyl)-N-(3-methyl-4-tert.butoxycarbonyl-phenyl)-acetamide are dissolved in 50 ml of dichloromethane and combined with 10 ml of trifluoroacetic acid at 20°C. After 4 hours at ambient temperature the solvent is distilled off, the residue is triturated with water and suction filtered.

Yield: 3.8 g (97 % of theoretical),

R_f value: 0.3 (silica gel; petroleum ether/ethyl acetate/glacial acetic acid = 1:1:0.01)

i. (L)-2-(5-Cyano-2-benzyloxy-phenyl)-N-[3-methyl-4-(2-aminocarbonyl-pyrrolidin-1-yl-carbonyl)-phenyl]-acetamide

1.3 g (3.2 mmol) of 2-(5-cyano-2-benzyloxy-phenyl)-N-(3-methyl-4-carboxy-phenyl)-acetamide are dissolved in 55 ml of tetrahydrofuran and after the addition of 635 mg (3.9 mmol) of N,N'-carbonyldiimidazole stirred for 1 hour at 30 °C. Then 720 mg (6.4 mmol) of L-prolinamide are added at ambient temperature. After 18 hours the solvent is distilled off and the residue is chromatographed on silica gel, eluting with ethyl acetate.

Yield: 0.32 g (20 % of theoretical),

R_f value: 0.15 (silica gel; ethyl acetate + 1 drop of glacial acetic acid)

k. (L)-2-(5-carbamimidoyl-2-benzyloxy-phenyl)-N-[3-methyl-4-(2-aminocarbonyl-pyrrolidin-1-yl-carbonyl)-phenyl]-acetamide-hydrochloride

300 mg (0.6 mmol) of (L)-2-(5-cyano-2-benzyloxy-phenyl)-N-[3-methyl-4-(2-amino-carbonyl-pyrrolidin-1-yl-carbonyl)-phenyl]-acetamide are dissolved in 15 ml of saturated ethanolic hydrochloric acid and stirred for 17 hours at ambient temperature. The solvent is distilled off, the residue is dissolved in 20 ml of absolute ethanol and combined with 600 mg (6.2 mmol) of ammonium carbonate. After 22 hours the mixture is evaporated to dryness. The residue is combined with ethanol, the insoluble inorganic salts are suction filtered, the filtrate is combined with ether and the product precipitated is suction filtered.

Yield: 0.18 g (54 % of theoretical),

R_f value: 0.5 (Reversed Phase RP 8; 5% sodium chloride solution/methanol = 2:3)

l. (L)-2-(5-carbamimidoyl-2-hydroxy-phenyl)-N-[3-methyl-4-(2-aminocarbonyl-pyrrolidin-1-yl-carbonyl)-phenyl]-acetamide-hydrochloride

Prepared analogously to Example 1.f. from (L)-2-(5-carbamimidoyl-2-benzyloxy-phenyl)-N-[3-methyl-4-(2-aminocarbonyl-pyrrolidin-1-yl-carbonyl)-phenyl]-acetamide-hydrochloride and palladium on activated charcoal/hydrogen in ethanol.

Yield: 74 % of theoretical,

R_f value: 0.73 (Reversed Phase RP 8; 5% sodium chloride solution/methanol = 2:3)

$C_{22}H_{25}N_5O_4$ x HCl (423.48/459.94)

Mass spectrum : $(M+H)^+$ = 424

$(M-H)^-$ = 422

Example 2

2-(5-carbamimidoyl-2-hydroxy-phenyl)-N-{3-methyl-4-(2-tert.butoxycarbonylamino-methyl-piperidin-1-yl-carbonyl)-phenyl}-acetamide-hydrochloride

a. 2-(5-Cyano-2-benzyloxy-phenyl)-N-{3-methyl-4-(2-tert.butyloxycarbonylamino-methyl-piperidin-1-yl-carbonyl)-phenyl}-acetamide

Prepared analogously to Example 1.i. from 2-(5-cyano-2-benzyloxy-phenyl)-N-(3-methyl-4-carboxy-phenyl)-acetamide and tert.-butyloxycarbonylaminomethyl-piperidine/ O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate.

Yield: 79 % of theoretical,

R_f value: 0.3 (silica gel;ethyl acetate/petroleum ether = 2:3)

b. 2-(5-N-hydroxycarbamimidoyl-2-benzyloxy-phenyl)-N-[3-methyl-4-(2-tert.butyloxy-carbonylaminomethyl-piperidin-1-yl-carbonyl)-phenyl]-acetamide

A solution of 0.73 g (1.22 mmol) of 2-(5-cyano-2-benzyloxy-phenyl)-N-[3-methyl-4-(2-tert.butyloxycarbonylaminomethyl-piperidin-1-yl-carbonyl)-phenyl]-acetamide and 175 mg (2.5 mmol) of hydroxylamine hydrochloride in 50 ml of methanol is combined with a solution of 1.2 g (3.7 mmol) of caesium carbonate in 1.0 ml of water and refluxed for 18 hours. After cooling the crude product is purified on silica gel, eluting with dichloromethane/ ethanol (98:2) plus 2% glacial acetic acid. The uniform fractions are combined and evaporated down.

Yield: 0.46 g (38% of theoretical),

R_f value: 0.46 (silica gel, dichloromethane/ethanol = 1:1 + glacial acetic acid)

c. 2-(5-carbamimidoyl-2-hydroxy-phenyl)-N-[3-methyl-4-(2-tert.butyloxycarbonyl-aminomethyl-piperidin-1-yl-carbonyl)-phenyl]-acetamide

Prepared analogously to Example 1.f. from 2-(5-N-hydroxycarbamimidoyl-2-benzyloxy-phenyl)-N-[3-methyl-4-(2-tert.butyloxycarbonylaminomethyl-piperidin-1-yl-carbonyl)-phenyl]-acetamide and palladium on activated charcoal (20%) in glacial acetic acid.

Yield: 25% of theoretical

R_f value: 0.46 (Reversed Phase RP 8; 5% sodium chloride solution/methanol = 2:3)

$C_{28}H_{37}N_5O_5$ x HCl (523.64/560.09)

Mass spectrum : $(M+H)^+$ = 524

Example 3

2-(5-aminomethyl-2-hydroxy-phenyl)-N-[3-methyl-4-(pyrrolidin-1-yl-carbonyl)-phenyl]-acetamide

a. 2-(5-aminomethyl-2-benzyloxy-phenyl)-N-[3-methyl-4-(pyrrolidin-1-yl-carbonyl)-phenyl]-acetamide

300 mg (0.66 mmol) of 2-(5-cyano-2-benzyloxy-phenyl)-N-[3-methyl-4-(pyrrolidin-1-yl-carbonyl)-phenyl]-acetamide are dissolved in 30 ml of methanolic ammonia solution and after the addition of 300 mg of Raney nickel hydrogenated for 5 hours with hydrogen (5 atmospheres) at ambient temperature. The catalyst is filtered off and the filtrate is evaporated down.

Yield: 250 mg (79% of theoretical),

R_f value: 0.43 (silica gel; dichloromethane/ethanol = 8:2 + ammonia)

b. 2-(5-aminomethyl-2-hydroxy-phenyl)-N-[3-methyl-4-(pyrrolidin-1-yl-carbonyl)-phenyl]-acetamide

Prepared analogously to Example 1.f. from 2-(5-aminomethyl-2-benzyloxy-phenyl)-N-[3-methyl-4-(pyrrolidin-1-yl-carbonyl)-phenyl]- acetamide and hydrogen/palladium on activated charcoal in methanol.

Yield: 54 % of theoretical,

R_f value: 0.16 (silica gel; dichloromethane/ethanol = 8:2)

$C_{21}H_{25}N_3O_3$ (367.45)

Mass spectrum : $(M-H)^-$ = 366

Example 4

2-(3-carbamimidoyl-phenyl)-N-[3-methyl-4-(pyrrolidin-1-yl-carbonyl)-phenyl]-2,2-dimethylacetamide-hydrochloride

a. methyl 2-(3-cyano-phenyl)-2-methyl-propionate

A solution of 2.5 g (15.4 mmol) of 3-cyanophenylacetic acid in 5 ml dimethyl sulphoxide is added dropwise at 5°C to a suspension of 1.9 g (48 mmol) of sodium hydride in 100 ml dimethyl sulphoxide. After 10 minutes 3 ml (47.7 mmol) of methyl iodide are added. After 1 hour at ambient temperature the reaction solution is poured onto ice water, adjusted to pH 5 with glacial acetic acid and extracted with ethyl acetate. The combined organic extracts are dried and evaporated down. The crude product is chromatographed on silica gel, eluting with dichloromethane.

Yield: 2.4 g (77 % of theoretical),

R_f value: 0.8 (silica gel; petroleum ether/ethyl acetate = 1:1)

b. 2-(3-cyano-phenyl)-2-methyl-propionic acid

2.4 g (11.5 mmol) of methyl 2-(3-cyano-phenyl)-2-methyl-propionate are dissolved in 16 ml of tetrahydrofuran, combined with a solution of 1 g (23.8 mmol) of lithium hydroxide in 20 ml of water and stirred for 20 hours at ambient temperature. The tetrahydrofuran is distilled off, the residue is adjusted to pH 4 with hydrochloric acid and extracted with ethyl acetate. The combined organic extracts are dried and evaporated down.

Yield: 1.5 g (66 % of theoretical),

R_f value: 0.3 (silica gel; petroleum ether/ethyl acetate = 1:1)

c. 2-(3-cyano-phenyl)-N-[3-methyl-4-(pyrrolidin-1-yl-carbonyl)-phenyl]- 2,2-dimethylacetamide

Prepared analogously to Example 1.g. from 2-(3-cyano-phenyl)-2-methyl-propionic acid, O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate, N-methylmorpholine and 3-methyl-4-(pyrrolidin-1-yl-carbonyl)-aniline in dimethylformamide.

Yield: 82 % of theoretical,

R_f value: 0.35 (silica gel; dichloromethane/ethanol = 19:1)

d. 2-(3-carbamimidoyl-phenyl)-N-[3-methyl-4-(pyrrolidin-1-yl-carbonyl)-phenyl]- 2,2-dimethylacetamide -hydrochloride

Prepared analogously to Example 1.k. from 2-(3-cyano-phenyl)-N-[3-methyl-4-(pyrrolidin-1-yl-carbonyl)-phenyl]- 2,2-dimethylacetamide and hydrochloric acid/ammonium carbonate in ethanol.

Yield: 54 % of theoretical,

R_f value: 0.35 (silica gel; dichloromethane/ethanol/glacial acetic acid = 8:2:0.2)

$C_{23}H_{28}N_4O_2$ x HCl (392.51/428.97)

Mass spectrum : $(M+H)^+$ = 393

$(M+Cl)^-$ = 427/29 (Cl)

Example 5

2-(5-carbamimidoyl-2-ethoxycarbonylmethyloxy-phenyl)-N-[3-methyl-4-(pyrrolidin-1-yl-carbonyl)-phenyl]-acetamide-hydrochloride

a. 2-(5-cyano-2-ethoxycarbonylmethyloxy-phenyl)-N-[3-methyl-4-(pyrrolidin-1-yl-carbonyl)-phenyl]-acetamide

0.3 g (0.8 mmol) of 2-(5-cyano-2-hydroxy-phenyl)-N-[3-methyl-4-(pyrrolidin-1-yl-carbonyl)-phenyl]-acetamide are dissolved in 20 ml of acetone and after the addition of 276 mg (2 mmol) of potassium carbonate stirred for 15 minutes at ambient temperature. Then 0.1 ml (0.9 mmol) of ethyl bromoacetate are added. After 1 hour at 40°C the reaction solution is stirred in ice water and extracted with ethyl acetate. The combined organic extracts are dried, evaporated down and crystallised with ether/petroleum ether.

Yield: 0.22 g (59 % of theoretical),

R_f value: 0.4 (silica gel; dichloromethane/ethanol = 19:1)

b. 2-(5-carbamimidoyl-2-ethoxycarbonylmethyloxy-phenyl)-N-[3-methyl-4-(pyrrolidin-1-yl-carbonyl)-phenyl]-acetamide-hydrochloride

Prepared analogously to Example 1.k. from 2-(5-cyano-2-ethoxycarbonylmethyloxy-phenyl)-N-[3-methyl-4-(pyrrolidin-1-yl-carbonyl)-phenyl]-acetamide and hydrochloric acid/ammonium carbonate in ethanol.

Yield: 73 % of theoretical,

R_f value: 0.35 (Reversed Phase RP 8; 5% sodium chloride solution/methanol = 2:3)

$C_{25}H_{30}N_4O_5$ x HCl (466.54/503.00)

Mass spectrum : $(M+H)^+$ = 467

$(M+Cl)^-$ = 501/03 (Cl)

Example 6

2-(5-carbamimidoyl-2-carboxymethyloxy-phenyl)-N-[3-methyl-4-(pyrrolidin-1-yl-carbonyl)-phenyl]-acetamide-hydrochloride

0.12 g (0.24 mmol) of 2-(5-carbamimidoyl-2-ethoxycarbonylmethyloxy-phenyl)-N-[3-methyl-4-(pyrrolidin-1-yl-carbonyl)-phenyl]-acetamide-hydrochloride are stirred in 10 ml of 6 molar hydrochloric acid for 16 hours at ambient temperature. Then the solvent is distilled off, the residue combined with acetone and ether and again evaporated to dryness.

Yield: 42 mg (37 % of theoretical),

R_f value: 0.45 (Reversed Phase RP 8; 5% sodium chloride solution/methanol = 2:3)

$C_{23}H_{26}N_4O_5$ x HCl (438.49/474.95)

Mass spectrum : $(M+H)^+$ = 439

$(M-H)^-$ = 437

Example 7

2-(5-carbamimidoyl-2-hydroxy-phenyl)-N-[3-methyl-4-(piperidin-3-yl-carbonyl)-phenyl]-acetamide

a. 3-methyl-4-(pyridin-3-yl-carbonyl)-aniline

14.9 g (111.6 mmol) of aluminium chloride, 4.2 g (27.8 mmol) of 3-methylacetanilide and 9.9 g (55.8 mmol) of nicotinyl chloride-hydrochloride are stirred for 2 hours at

100 °C. The reaction mixture is stirred into ice water while still hot and extracted with ethyl acetate. The combined organic extracts are dried and evaporated down. The residue is stirred for 1.5 hours at 100°C with 50 ml of 6 molar hydrochloric acid. Then it is cooled, adjusted to pH 8 with ammonia and extracted with dichloromethane. The organic phase is evaporated down and purified on silica gel, eluting with dichloromethane/methanol (1-4%).
Yield: 1.4 g (24 % of theoretical),
R_f value: 0.4 (silica gel; dichloromethane/ethanol = 19:1)

b. 2-(5-cyano-2-benzyloxy-phenyl)-N-[3-methyl-4-(pyridin-3-yl-carbonyl)-phenyl]-acetamide

Prepared analogously to Example 1.g. from 3-methyl-4-(pyridin-3-yl-carbonyl)-aniline, (2-benzyloxy-5-cyanophenyl)-acetic acid, O-(benzotriazol-1-yl)-N,N,N',N'-tetra-methyluronium tetrafluoroborate and N-methylmorpholine in dimethylformamide.
Yield: 56 % of theoretical,
R_f value: 0.8 (silica gel; ethyl acetate/ethanol = 9:1)

c. 2-(5-carbamimidoyl-2-benzyloxy-phenyl)-N-[3-methyl-4-(pyridin-3-yl-carbonyl)-phenyl]-acetamide

Prepared analogously to Example 1.k. from 2-(5-cyano-2-benzyloxy-phenyl)-N-[3-methyl-4-(pyridin-3-yl-carbonyl)-phenyl]-acetamide and hydrochloric acid/ammonium carbonate in ethanol.
Yield: 44 % of theoretical,
R_f value: 0.2 (silica gel; dichloromethane/ethanol/glacial acetic acid = 8:2:0.2)

d. 2-(5-carbamimidoyl-2-hydroxy-phenyl)-N-[3-methyl-4-(piperidin-3-yl-carbonyl)-phenyl]-acetamide

0.32 g (0.6 mmol) of 2-(5-carbamimidoyl-2-benzyloxy-phenyl)-N-[3-methyl-4-(pyridin-3-yl-carbonyl)-phenyl]-acetamide are dissolved in 75 ml methanol, adjusted to pH 8 with 0.5 ml conc. ammonia and after the addition of 0.15 g palladium on activated charcoal (10%) hydrogenated for 70 minutes at ambient temperature with hydrogen. Then the catalyst is filtered off and the filtrate is evaporated down. The residue is

stirred with ethyl acetate/ether/ petroleum ether (1:1:1) and the crystalline product is suction filtered.

Yield: 0.13 g (55 % of theoretical),

R_f value: 0.7 (Reversed Phase RP 8; 5% sodium chloride solution/methanol = 1:1)

$C_{22}H_{26}N_4O_3$ (394.47)

Mass spectrum : $(M+H)^+$ = 395

$(M-H)^-$ = 393

The following compounds are prepared analogously to Example 7:

(1) 2-(5-carbamimidoyl-2-hydroxy-phenyl)-N-(3-methyl-4-benzoyl-phenyl)-acetamide-hydrochloride

Yield: 12 % of theoretical,

R_f value: 0.4 (silica gel; dichloromethane/ethanol = 7:3 + 1% glacial acetic acid)

$C_{23}H_{21}N_3O_3$ x HCl (387.44/423.90)

Mass spectrum : $(M+H)^+$ = 388

$(M-H)^-$ = 386

(2) 2-(5-carbamimidoyl-2-hydroxy-phenyl)-N-[3-methyl-4-(hydroxy-phenyl-methyl)-phenyl]-acetamide-hydrochloride

Yield: 23 % of theoretical,

R_f value: 0.35 (silica gel; dichloromethane/ethanol = 7:3 + 1% glacial acetic acid)

$C_{23}H_{23}N_3O_3$ x HCl (389.46/425.92)

Mass spectrum : $(M+H)^+$ = 390

$(M-H)^-$ = 388

(3) 2-(5-carbamimidoyl-2-hydroxy-phenyl)-N-{4-[(3-carbamimidoyl-phenyl)-hydroxy-methyl]-3-methyl-phenyl}-acetamide-dihydrochloride

Yield: 37 % of theoretical,

R_f value: 0.25 (Reversed Phase RP 8; 5% sodium chloride solution/methanol = 2:3)

$C_{24}H_{25}N_5O_3$ x 2 HCl (431.50/504.42)

Mass spectrum : $(M+H)^+$ = 432

Example 8

2-(5-carbamimidoyl-2-hydroxy-phenyl)-N-[3-methyl-4-(pyrrolidin-1-yl-carbonyl)-phenyl]- 2,2-dimethylacetamide -hydrochloride

a. 3-(1,1-Dimethyl-allyl)-4-hydroxy-benzonitrile

25 g (0.13 mol) of 4-(3-methyl-but-2-enyloxy)-benzonitrile are refluxed in 250 ml dimethylformamide for 90 hours. The solvent is distilled off and the residue is taken up in ethyl acetate/water. The organic phase is dried and evaporated down. The residue is dissolved in toluene and extracted with 2 molar sodium hydroxide solution. The aqueous phase is filtered through activated charcoal and acidified with glacial acetic acid. The precipitate formed is suction filtered and dried.

Yield: 1.8 g (7 % of theoretical),

R_f value: 0.53 (silica gel; petroleum ether/ethyl acetate = 7:3)

b. 4-benzyloxy-3-(1,1-dimethyl-allyl)-benzonitrile

Prepared analogously to Example 1.c. from 3-(1,1-dimethyl-allyl)-4-hydroxy-benzonitrile, benzyl bromide and potassium carbonate in dimethylformamide.

Yield: 93 % of theoretical,

R_f value: 0.70 (silica gel; petroleum ether/ethyl acetate = 7:3)

c. 2-(2-benzyloxy-5-cyano-phenyl)-2-methyl-propionic acid

2.2 g (7.9 mmol) of 4-benzyloxy-3-(1,1-dimethyl-allyl)-benzonitrile are dissolved in 60 ml acetonitrile and after the addition of a solution of 11.9 g (55.6 mmol) of sodium metaperiodate and 50 mg (0.24 mmol) of ruthenium-(III)-chloride in 80 ml of water stirred for 4.5 hours at 45°C. After dilution with ethyl acetate, the organic phase is separated off and evaporated down. The residue is dissolved in dichloromethane and extracted with 1 molar sodium hydroxide solution. The aqueous phase is filtered through activated charcoal, the filtrate is poured onto 400 ml of 6 molar hydrochloric acid and 200 g of ice. The precipitate is suction filtered and dried.

Yield: 0.95 g (41 % of theoretical),

R_f value: 0.22 (silica gel; petroleum ether/ethyl acetate/glacial acetic acid = 7:3:0.1)

d. 2-(2-benzyloxy-5-cyano-phenyl)-2-methyl-propionic acid chloride

510 mg (1.73 mmol) of 2-(2-benzyloxy-5-cyano-phenyl)-2-methyl-propionic acid are dissolved in 10 ml dichloromethane and after the addition of 0.38 ml (5.21 mmol) of thionyl chloride and 0.1 ml of dimethylformamide heated to 50°C for 2.5 hours. Then the reaction mixture is evaporated down and further reacted without purification.

Yield: 530 mg (98 % of theoretical).

e. 2-(2-benzyloxy-5-cyano-phenyl)-N-[3-methyl-4-(pyrrolidin-1-yl-carbonyl)-phenyl]-2,2-dimethylacetamide

A solution of 390 mg (1.9 mmol) of 3-methyl-4-(pyrrolidin-1-yl-carbonyl)-aniline in 50 ml of tetrahydrofuran is combined with 0.7 ml (5.18 mmol) of triethylamine. Then a solution of 530 mg (1.69 mmol) of 2-(2-benzyloxy-5-cyano-phenyl)-2-methyl-propionic acid chloride in 20 ml of tetrahydrofuran is added dropwise. After 14 hours at ambient temperature the solvent is evaporated off and the residue is purified on silica gel, eluting with ethyl acetate/petroleum ether (4:1).

Yield: 410 mg (50 % of theoretical),

R_f value: 0.38 (silica gel; ethyl acetate)

f. 2-(5-carbamimidoyl-2-hydroxy-phenyl)-N-[3-methyl-4-(pyrrolidin-1-yl-carbonyl)-phenyl]- 2,2-dimethylacetamide -hydrochloride

Prepared analogously to Example 1.k. from 2-(2-benzyloxy-5-cyano-phenyl)-N-[3-methyl-4-(pyrrolidin-1-yl-carbonyl)-phenyl]- 2,2-dimethylacetamide and hydrochloric acid/ammonium carbonate in ethanol followed by reaction with hydrogen/palladium on activated charcoal in methanol analogously to Example 1.l..

Yield: 77 % of theoretical,

R_f value: 0.5 (Reversed Phase RP 8; 5% sodium chloride solution/methanol = 2:3)

$C_{23}H_{28}N_4O_3$ x HCl (408.50/444.96)

Mass spectrum : $(M+H)^+$ = 409

$(M-H)^-$ = 407

Example 9

2-(5-carbamimidoyl-2-hydroxy-phenyl)-N-[3-chloro-4-(pyrrolidin-1-yl-carbonyl)-phenyl]-acetamide-hydrochloride

a. 3-chloro-4-(pyrrolidin-1-yl-carbonyl)-nitrobenzene

Prepared analogously to Example 1.g. from 2-chloro-4-nitrobenzoic acid, O-(benzotriazol-1-yl)-N,N,N'-N'-tetramethyluronium fluoroborate, N-ethyl-diisopropylamine and pyrrolidine in tetrahydrofuran/water 9:1.
Yield: 72 % of theoretical,
R_f value: 0.65 (silica gel; dichloromethane/ethanol = 95:5)

b. 3-chloro-4-(pyrrolidin-1-carbonyl)-aniline

Prepared analogously to Example 1.f. from 3-chloro-4-(pyrrolidin-1-yl-carbonyl)-nitrophenol and hydrogen/palladium on activated charcoal in methanol/dichloromethane (1:1).
Yield: 100 % of theoretical,
R_f value: 0.42 (silica gel; dichloromethane/ethanol = 95:5)

c. 2-(2-benzyloxy-5-cyano-phenyl)-N-[3-chloro-4-(pyrrolidin-1-yl-carbonyl)-phenyl]-acetamide

Prepared analogously to Example 8.e. from 3-chloro-4-(pyrrolidin-1-yl-carbonyl)-aniline, (2-benzyloxy-5-cyanophenyl)-acetic acid chloride and triethylamine in tetrahydrofuran.
Yield: 64 % of theoretical,
R_f value: 0.75 (silica gel; dichloromethane/ethanol = 95:5)

d. 2-(5-carbamimidoyl-2-hydroxy-phenyl)-N-[3-chloro-4-(pyrrolidin-1-yl-carbonyl)-phenyl]-acetamide-hydrochloride

Prepared analogously to Example 1.k. from 2-(2-benzyloxy-5-cyano-phenyl)-N-[3-chloro-4-(pyrrolidin-1-yl-carbonyl)-phenyl]-acetamide and hydrochloric acid/ammonium carbonate in ethanol followed by reaction with hydrogen/palladium on activated charcoal in methanol analogously to Example 1.l..

Yield: 50 % of theoretical,

R_f value: 0.5 (Reversed Phase RP 8; methanol/5% sodium chloride solution = 3:2)

$C_{20}H_{21}ClN_4O_3$ x HCl (400.87/437.33)

Mass spectrum :	$(M+H)^+$	= 401
	$(M-H)^-$	= 399
	$(M+Cl)^-$	= 435/37 (Cl)

Example 10

Dry ampoule containing 75 mg of active substance per 10 ml

Composition:

Active substance	75.0 mg
Mannitol	50.0 mg
water for injections	ad 10.0 ml

Preparation:

Active substance and mannitol are dissolved in water. After packaging the solution is freeze-dried. To produce the solution ready for use, the product is dissolved in water for injections.

Example 11

Dry ampoule containing 35 mg of active substance per 2 ml

Composition:

Active substance	35.0 mg
Mannitol	100.0 mg
water for injections	ad 2.0 ml

Preparation:

Active substance and mannitol are dissolved in water. After packaging, the solution is freeze-dried.

To produce the solution ready for use, the product is dissolved in water for injections.

Example 12

Tablet containing 50 mg of active substance

Composition:

(1) Active substance	50.0 mg
(2) Lactose	98.0 mg
(3) Maize starch	50.0 mg
(4) Polyvinylpyrrolidone	15.0 mg
(5) Magnesium stearate	2.0 mg
	215.0 mg

Preparation:

(1), (2) and (3) are mixed together and granulated with an aqueous solution of (4). (5) is added to the dried granulated material. From this mixture tablets are pressed, biplanar, faceted on both sides and with a dividing notch on one side.
Diameter of the tablets: 9 mm.

Example 13

Tablet containing 350 mg of active substance

Composition:

(1) Active substance	350.0 mg
(2) Lactose	136.0 mg
(3) Maize starch	80.0 mg
(4) Polyvinylpyrrolidone	30.0 mg
(5) Magnesium stearate	4.0 mg
	600.0 mg

Preparation:
(1), (2) and (3) are mixed together and granulated with an aqueous solution of (4). (5) is added to the dried granulated material. From this mixture tablets are pressed, biplanar, faceted on both sides and with a dividing notch on one side.
Diameter of the tablets: 12 mm.

Example 14

Capsules containing 50 mg of active substance

Composition:

(1) Active substance	50.0 mg
(2) Dried maize starch	58.0 mg
(3) Powdered lactose	50.0 mg
(4) Magnesium stearate	2.0 mg
	160.0 mg

Preparation:
(1) is triturated with (3). This trituration is added to the mixture of (2) and (4) with vigorous mixing.
This powder mixture is packed into size 3 hard gelatine capsules in a capsule filling machine.

Example 15

Capsules containing 350 mg of active substance

Composition:

(1) Active substance	350.0 mg
(2) Dried maize starch	46.0 mg
(3) Powdered lactose	30.0 mg
(4) Magnesium stearate	4.0 mg
	430.0 mg

Preparation:
(1) is triturated with (3). This trituration is added to the mixture of (2) and (4) with vigorous mixing.

This powder mixture is packed into size 0 hard gelatine capsules in a capsule filling machine.

Example 16

Suppositories containing 100 mg of active substance

1 suppository contains:

Active substance	100.0 mg
Polyethyleneglycol (M.W. 1500)	600.0 mg
Polyethyleneglycol (M.W. 6000)	460.0 mg
Polyethylenesorbitan monostearate	840.0 mg
	2,000.0 mg

Preparation:

The polyethyleneglycol is melted together with polyethylenesorbitan monostearate. At 40°C the ground active substance is homogeneously dispersed in the melt. This is then cooled to 38°C and poured into slightly chilled suppository moulds.